OBSTETRICS

Why the term neonatal encephalopathy should be preferred over neonatal hypoxic-ischemic encephalopathy

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The unresponsiveness of the full-term newborn is sometimes attributed to asphyxia, even when no severe physiologic disturbance occurred during labor and delivery. The controversy about whether to use the name "hypoxic-ischemic encephalopathy" or "newborn encephalopathy" has recently flared in publications directed toward pediatricians and neurologists. In this clinic opinion piece, I discuss the importance to obstetricians of this decision and explain why "newborn encephalopathy" should be the default term.

Key words: asphyxia, central nervous system diseases, diagnosis, diseases, infant, newborn

A full term newborn enters the world unresponsive to stimuli. Should the diagnosis be "hypoxic-ischemic encephalopathy" (HIE) or "newborn encephalopathy" (NE)? Although the controversy about which label to use has been going on for more than 2 decades,[1] it has escalated recently in the pediatric[2] and neurology[3] literatures. I wrote this opinion piece to bring the controversy to the obstetric literature where it belongs. The diagnostic labels you and the neonatologist apply to each child have potential consequences for each of you, the family, the hospital, and its employees.

The voice of a distinguished author can carry inappropriate weight, and thereby influence those who read, "I believe that we have an obligation to provide the most accurate information that we can in a given infant concerning the nature and extent of the neuropathology, the likely cause, the most probable outcome, and the best available therapy. Thus, I feel strongly that neonatal HIE, and not a vague designation (NE) is the appropriate terminology for the encephalopathy seen in term infants.[3]

This clinical opinion essay provides another perspective. The diagnosis of HIE is appropriate when the cerebral blood flow is documented to be sufficiently reduced, the oxygen content of the blood delivered to the brain is below a level needed to avoid energy failure in brain cells, and brain metabolism is so low that cell integrity cannot be maintained. However, such assessments of the fetus or the newborn are not yet routinely available.

These limitations have prompted a reliance on biomarkers of exposure to presumed hypoxia and ischemia near the time of birth. Unfortunately, they do less well than desired differentiating term infants who develop NE from those who do not.[4] For example, only about one quarter of children who had a base excess of −10 mml/L. Thirty to 45 minutes after birth fulfilled criteria for NE.[5] A base excess of −14 mmol/L, however, had a sensitivity of 73% and a specificity of 82% for identifying NE.

Despite the hope that electronic fetal monitoring would help reduce the occurrence of cerebral palsy,[6] identify newborns whose base excess has surpassed an unacceptable level (eg, >−12 mmol/L),[7] or provide knowledge of the duration, mechanism, and severity of hypoxia and occasionally, the timing of neurologic injury,[8] these hopes have yet to be realized. Cardiotocographic abnormalities (including bradycardia, decreased variability, nonreactivity, and variable decelerations) are not good predictors of severe metabolic acidosis.[9] Even advances in cardiotocography with ST waveform analysis do not appear to predict NE[10,11] or metabolic acidosis at birth.[10,12]

In the presence of a nonreassuring fetal heart rate pattern, fetal scalp lactate sampling does not appear to improve the clinician's ability to reduce the occurrence of NE.[13] This observation leads to the inference that the clinician's response to fetal acidemia does not minimize brain damage.

In light of these observations, the only surrogate of cerebral oxygen use that currently provides some discriminating information is an extremely low base excess. Severely low base excess, however, should be seen as having its own set of antecedents.[14]

I address only 5 points, what constitutes a cause, the evidence that hypoxic-ischemic exposures contribute to the newborn's unresponsiveness, the evidence that other characteristics and exposures contribute to this situation, how attributing an unfortunate occurrence to a proceeding event, characteristic, or exposure is fraught with biases, and the consequences of using one diagnostic label or another.

What constitutes a cause?

Epidemiologists continue to argue about what constitutes a cause.[15-18] The general consensus, however, is that single-cause attribution is almost never correct, and that variants of the multiple causation model are likely to be most helpful.[19-23] Even the current proponent of HIE accepts the concept of multiple causation models.[24]

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Received June 8, 2012; revised July 13, 2012; accepted July 19, 2012.

The author reports no conflict of interest.

Reprints not available from the author.

0002-9378/free

http://dx.doi.org/10.1016/j.ajog.2012.07.020

I am not aware of epidemiologists or thoughtful biologists who accept a deterministic model of disease causation that implies if A occurs, then B will invariably follow.[25,26] Rather, a probabilistic model is the norm, which has the characteristic that if A occurs, then the risk of B is increased.[27] The sufficient component view of disease causation holds that a disease will occur only when sufficiently many of the contributions are present.[28]

Epidemiologists who conduct observational studies tend to be wary of implying causation.[27] Rather, we tend to talk about associations and contributors to models of disease occurrence. Universal acceptance of a set of criteria for what constitutes a cause has yet to be achieved.[15, 29-31]

These causal inference limitations have not dissuaded task forces of distinguished organizations from trying to establish causal relationships between sets of delivery and newborn characteristics and brain damage in the newborn.[32-34] The results of these attempts, however, have been less than satisfying. For example, among neonates with a sentinal event characterized by a sudden prolonged fetal heart rate deceleration that lasted until delivery, only 10% of the neonates demonstrated all 4 of the criteria offered by the American College of Obstetrics and Gynecology task force[32] to relate perinatal events to the subsequent development of cerebral palsy.[35] Only 2 of 46 children born at term who developed cerebral palsy satisfied criteria established by the American College of Obstetricians and Gynecologists together with the American Academy of Pediatrics[34] to identify acute intrapartum hypoxia.[36]

The worth of the causal criteria tabulated by authoritative task forces remains to be established. Limitations of the latest task force's recommendations prompted the creation of what was hoped would be an improved classification of cardiotocographic abnormalities.[37] Nevertheless, even these efforts have been challenged.[38] An assessment of how well the proposed graded classification of fetal heart rate tracings predicted neonatal metabolic acidosis and NE is limited by the addition of medicolegal cases to an unselected sample.[39]

In the absence of universally accepted guidelines, the extent of the encephalopathy should be described,[40] and consideration given to hypothermia and other therapies intended to minimize the extent of brain damage.[41]

Multihit models of brain damage

Cancer epidemiology benefited considerably from the concept of what was at first a 2-hit model of cancer biology, and extended to become the multihit model.[42, 43] In these models, no single exposure, results in damage. Rather, multiple exposures, each at an intensity incapable of causing damage by itself, are needed to result in any damage. To some extent, the multiple-cause model of brain damage in the newborn is just this kind of multihit model with no single exposure sufficient to result in appreciable damage.[44]

"Sensitization" is the name given to the phenomenon of one low-intensity (ie, subdamaging) exposure allowing a subsequent subdamaging exposure to result in damage. For example, in 7-day old rats, short periods of hypoxia—ischemia that by themselves cause no or little injury, will result in obvious injury if the animals were given a low dose of intraperitoneal endotoxin 4 hours[45] or 72 hours[46] earlier. This phenomenon of preceding inflammation increasing the brain damage caused by subsequent damage-promoting exposures is supported by other studies.[47-53]

In the human born at term, the multihit model appears to apply to the risk of NE,[54-56] as well as retinopathy of prematurity.[57] The multihit model might also apply to brain damage in the preterm human newborn, but it is not yet clear if the potentially damaging exposures are prolonged or recurrent.[58-60] The obvious inference is that in some situations, multiple exposures are needed to result in damage.[61-65]

"Causes" of unresponsiveness at birth

When many of us use the term "newborn encephalopathy," we make no assumption about a hypoxic-ischemic etiology.[1,66,67] The assumption that only intrapartum hypoxia-ischemia causes an infant to be limp and unresponsive at birth is not supported by epidemiologic studies, which show that increased risk of NE is associated with a variety of maternal characteristics (low hemoglobin, low thyroxine concentrations, fever during labor), as well as fetal characteristics (severe growth restriction, persistent occiput-posterior position),[55,68-73] and placenta lesions.[74] Because other phenomena can contribute to the risk of NE, a single-attribution name should not be applied to an entity that probably has many "causes."[19]

A variety of gene mutations and congenital malformations of the brain in newborn rodents and humans have been associated with hypoventilation, frequent apneic episodes, and failure to increase breathing in response to hypoxemia and/or hypercarbia.[75-79] For example, a retrospective chart review of 48 individuals with Prader-Willi syndrome, 23% had asphyxia at birth, compared with an expected rate of 1%.[75]

Although some of these disorders first present during, or even after childhood, phenotypic variability can be prominent.[80] Indeed, these disorders have the potential to present with a picture indistinguishable from NE.[81]

Acidemia, sometimes considered an objective biomarker of asphyxia,[82,83] can be a reflection of metabolic disorders that are not a consequence of hypoxemia.[84] Nevertheless, some people have claimed to know when ischemia and hypoxemia occurred in unresponsive newborns.[85-87] Others of us recognize our limitations.

Our hesitancy is supported by the finding that after excluding newborns with chromosomal abnormalities and congenital malformations, the brain damage in term infants who appeared asphyxiated and encephalopathic before death at least 3 days after birth was consistent with onset before the start of labor.[88] One inference that follows from this is that an intrapartum sentinel event might not provide information about when the brain damage was initiated.

Perhaps biomarkers indicative of the intra-partum processes leading to brain damage might help distinguish evolving brain damage from other disorders with